

Early abnormal fibrinolysis and mortality in patients with thermal injury: a prospective cohort study

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Abstract

Introduction: Abnormal fibrinolysis early after injury has been associated with increased mortality in trauma patients, but no studies have addressed patients with burn injury. This prospective cohort study aimed to characterize fibrinolytic phenotypes in burn patients and to see if they were associated with mortality.

Methods: Patients presenting to a regional burn centre within 4 h of thermal injury were included. Blood was collected for sequential viscoelastic measurements using thromboelastography (RapidTEG™) over 12 h. The percentage decrease in clot strength 30 min after the time of maximal clot strength (LY30) was used to categorize patients into hypofibrinolytic/fibrinolytic shutdown (SD), physiological (PHYS) and hyperfibrinolytic (HF) phenotypes. Injury characteristics, demographics and outcomes were compared.

Results: Of 115 included patients, just over two thirds were male. Overall median age was 40 (i.q.r. 28–57) years and median total body surface area (TBSA) burn was 13 (i.q.r. 6–30) per cent. Some 42 (36.5 per cent) patients had severe burns affecting over 20 per cent TBSA. Overall mortality was 18.3 per cent. At admission 60.0 per cent were PHYS, 30.4 per cent were SD and 9.6 per cent HF. HF was associated with increased risk of mortality on admission (odds ratio 12.61 (95 per cent c.i. 1.12 to 142.57); $P=0.041$) but not later during the admission when its incidence also decreased. Admission SD was not associated with mortality, but incidence increased and by 4 h and beyond, SD was associated with increased mortality, compared with PHYS (odds ratio 8.27 (95 per cent c.i. 1.16 to 58.95); $P=0.034$).

Discussion: Early abnormal fibrinolytic function is associated with mortality in burn patients.

Introduction

The fibrinolytic system plays an important role in maintaining vascular patency by controlling the extension of the clot during haemostasis and mediating clot resolution¹. Early changes in fibrinolysis have important implications for patients with severe trauma. Moore and colleagues identified three fibrinolytic phenotypes, fibrinolytic shut-down (hypofibrinolytic), physiological (normal) and hyperfibrinolytic (deleted the word states), and found that an abnormal phenotype (hypo- or hyper-) at the time of arrival at a trauma centre was associated with increased risk of mortality². A study of 2540 severely injured adult patients found that 46 per cent presented with hypofibrinolysis, 36 per cent arrived with normal fibrinolysis and 18 per cent presented with hyperfibrinolysis³. Both hypo- and hyperfibrinolysis were associated with increased risks of mortality and a similar pattern has been identified in paediatric trauma patients⁴.

Plasma-based assays suggest that fibrinolysis may also be altered following thermal injury. The primary activator of fibrinolysis, tissue plasminogen activator, is elevated^{5,6}, as is its primary inhibitor, plasminogen activator inhibitor-1, following thermal injury^{5–10}. Plasminogen concentrations decline, reflecting activation to plasmin^{5,8,9,11}. Coincident with increased generation of plasmin, concentrations of the primary inhibitor of plasmin, alpha-2 antiplasmin, decline^{5,9,12}, as it complexes with plasmin for inactivation⁷. These early changes reflect the evolving balance between profibrinolytic and antifibrinolytic mechanisms. Numerous studies have also documented increased D-dimer concentrations, reflecting breakdown of fibrin or fibrinogen^{5,8,9,12–20}. It is clear that early dynamic fibrinolytic changes occur following burn injury.

Viscoelastic assays, such as thromboelastography (TEG), allow the real-time assessment of whole blood clotting function,

including fibrinolysis, thereby offering advantages over other assays in assessing the overall balance between coagulation and fibrinolysis¹⁸. A limited number of studies characterizing whole blood clotting function in patients with burn injury have been reported. Park and co-workers observed a hypercoagulable state and increasing fibrinolysis over the first 7 days after burn injuries with viscoelastic testing, that was not detected using standard coagulation assays¹⁸. Huzar and colleagues reported TEG data for 65 patients with at least 15 per cent total body surface area (TBSA) burn²¹. Some 60 per cent had a hypercoagulable state on admission, while 24 per cent were hypocoagulable. TEG values predicted 24-h resuscitation volumes, as well as plasma and platelet transfusions ($P < 0.050$).

Considering the early activation of both pro- and antifibrinolytic mechanisms early in the post-burn period, it seems likely that various fibrinolytic phenotypes may develop in burn patients, and that specific phenotypes may influence patient outcomes. It was hypothesized that patients with burn injury would display three early fibrinolytic phenotypes, and that these phenotypes might be related to mortality.

Methods

This was a prospective, observational study of patients with thermal injuries presenting to the MedStar Washington Hospital Burn Center, an American Burn Association verified regional burn centre. The Institutional Review Board of MedStar Health Research Institute and the Human Research Protections Office of the US Army Medical Research and Development Command approved this research. The requirement to obtain advanced written informed consent for emergency research was waived in accordance with US Code of Federal Regulations Title 21, Part 50 – Protection of Human Subjects, Subpart B – Informed Consent in Human Subjects and Section 50.24 – Exception from Informed Consent Requirement for Emergency Research. This study was conducted as part of the larger multicentre Systems Biology Coagulopathy of Trauma (SYSCOT) Research Program²².

Study population

Patients who presented within 4 h of thermal injury were screened for enrolment from October 2012 to March 2017. Patients with a history of coagulopathy, those taking anticoagulants, pregnant women, chemically injured patients, minors and patients not fluent in English or Spanish were excluded from the study. A total of 158 patients were enrolled and 115 included in the present analysis (Fig. 1, Table S1). Patients requiring formal burn resuscitation, typically those presenting with at least 15 per cent TBSA burns, underwent bodyweight and TBSA-guided resuscitation with Ringer's lactate titrated to adequate urine output from arrival for 24–48 h^{23,24}.

Clinical data

Clinical data were collected using standard case report forms and prespecified definitions for outcome variables. All physiological and clinical variables were recorded in REDCap^{25,26}.

Blood sampling

Blood samples for viscoelastic testing were collected in 3.2 per cent citrate tubes at the time of burn centre arrival/admission (time 0) and sequentially at 2, 4, 6, 8 and 12 h. Blood samples for clinical purposes were collected according to standard practice and analysed by the clinical laboratory for standard parameters, such as prothrombin time (PT) and international normalized

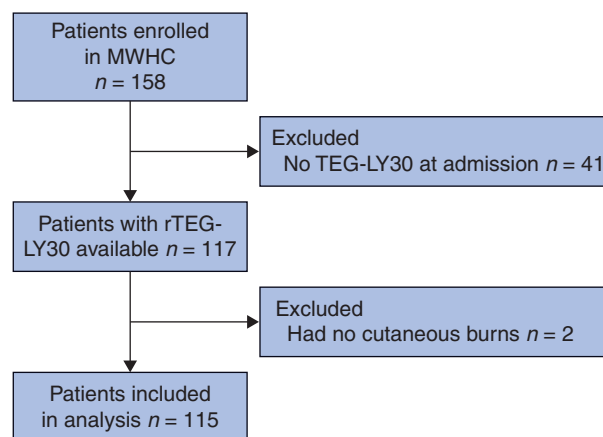


Fig. 1 Study cohort description

Patients without admission rapid thromboelastography measurement of clot lysis at 30 min after maximal clot strength (rTEG-LY30) and those without cutaneous burns were excluded from the present analysis. MWHC, MedStar Washington Hospital Center.

ratio (INR). Detailed sampling and other procedures have been described elsewhere²².

Viscoelastic testing

Viscoelastic properties of clot formation and clot lysis in whole blood samples were measured using the TEG[®] 5000 Thromboelastograph[®] (TEG, Haemonetics, Boston, Massachusetts, USA). Clotting was initiated using the RapidTEG[™] reagent, according to manufacturer instructions. TEG was performed using equipment and procedures certified by the College of American Pathologists. RapidTEG[™] incorporates activation of both the tissue factor and the factor XII pathways of blood coagulation to maximally activate clotting, and provides a rapid assessment of clot formation dynamics, clot strength and fibrinolysis. Clot lysis was determined by examining the percentage decrease in clot strength 30 min after the time of maximal clot strength. This parameter is referred to as LY30 and is a measure of fibrinolysis¹⁸. Other parameters reported for TEG included activated clotting time (ACT), α -angle and maximum amplitude (MA). The ACT, α -angle and MA are indicators of speed of clot initiation, rate of clot development and maximum clot strength, respectively.

Definitions of fibrinolytic phenotypes

Fibrinolytic phenotypes were characterized based on published findings documenting the existence of three distinct fibrinolytic phenotypes in non-burn trauma patients: hypofibrinolytic or fibrinolytic shut-down (SD), normal or physiological (PHYS) and hyperfibrinolytic (HF)^{2,27}. The following definitions derived from Stettler and co-workers were used: SD was defined as LY30 less than 0.6 per cent, PHYS as LY30 from 0.6 per cent to 7.7 per cent, and HF as LY30 greater than 7.7 per cent²⁷. Fibrinolytic phenotypes were determined at each sampling time point from 0 to 12 h.

Outcomes

The primary outcome measure was 30-day mortality. Secondary outcomes included intensive care unit (ICU) days, ventilator days and duration of hospital stay.

Statistical analysis

Descriptive statistics characterized the demographics and injuries of the patients. Categorical variables were summarized as frequencies and percentages and tested using χ^2 or Fisher's exact test for associations between survival status and the three fibrinolytic phenotypes. Continuous variables were expressed as median and interquartile ranges and tested using the Kruskal-Wallis test for comparing differences among fibrinolytic phenotypes when appropriate. Mann-Whitney U test with Bonferroni's correction was used for post hoc pairwise comparisons. Follow-up time was from admission until death, discharge or censoring on the 30th day after admission. Associations for the time to, or likelihood of, mortality were determined by uni- and multivariable Cox proportional hazards models (for computing hazard ratios (HRs)) and logistic regression models (for computing the odds ratios (ORs)). The Kolmogorov-type supremum test was used for the Cox proportional hazards assumption. Kaplan-Meier plots with log-rank tests were also used to characterize mortality based on fibrinolytic phenotype. Statistical significance was determined at the two-sided $P < 0.050$ level. All data analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Results

Demographics

Patient demographics and injury characteristics are presented in [Table 1](#). Patients were predominantly male (68.7 per cent) with a median age of 40 (i.q.r. 28–57) years. The median burn TBSA was 13.0 (i.q.r. 6–30) per cent and 42 (36.5 per cent) patients had severe burns (burn TBSA greater than 20 per cent). Overall mortality rate was 18.3 per cent (21 patients), and median time to death was 41.1 (i.q.r. 5.4–284.7) hours from admission ([Table 1](#)). Due to workflow constraints or early mortality, the number of patients with results for LY30 differed at the various time points. At hour 0 (admission) data were available for 115 patients, at later time points, data were available for between 70 and 97 patients.

Admission fibrinolytic phenotypes

At admission, 30.4 per cent of patients displayed the SD phenotype, 60.0 per cent were PHYS and 9.6 per cent were HF ([Table 1](#)). Patients with either the SD or HF phenotype were more likely to have burn TBSA greater than 20 per cent than those with the PHYS phenotype ($P = 0.047$) ([Table 1](#)). Burn TBSA greater than 20 per cent was associated with a higher proportion of patients with abnormal fibrinolysis (HF and SD combined) than burn TBSA 20 per cent or less (54.8 versus 31.5 per cent; $P = 0.010$). After adjustment for age, BMI, TBSA greater than or equal to or less than 20 per cent, total Glasgow coma score and inhalation injury, admission HF was associated with a nearly 13-fold higher risk of mortality (OR 12.61, 95 per cent c.i. 1.12 to 142.57; $P = 0.040$; [Table 2](#)) and a five-fold shorter time to death (HR 4.95; 95 per cent c.i. 1.17 to 20.95; $P = 0.030$; [Table 2](#) and [Fig. 2a](#)), compared with PHYS. Compared with admission PHYS, admission SD was not associated with increased mortality ($P = 0.256$).

Delayed fibrinolytic phenotypes

The percentage of surviving patients exhibiting the HF phenotype declined over time, while the percentage with SD increased ([Table 3](#)). HF was not associated with mortality at sampling times after time 0. Ten patients first developed the HF phenotype between 2 and 12 h after admission (delayed HF group), and one

subsequently died. The difference in mortality between this delayed HF group and patients that exhibited admission HF was not, however, statistically significant ($P = 0.064$). SD was associated with increased mortality at 4, 8 and 12 h ($P < 0.001$, 0.006 and 0.002, respectively) ([Table 3](#)).

Based on significance level, 4-hour delayed SD was selected for inclusion in more comprehensive models. Admission demographics and injury characteristics of patients alive at 4 h after admission for both SD and PHYS patients are shown in [Table S2](#). Patients that displayed the SD phenotype at 4 h had larger burns ($P < 0.001$), were more likely to be admitted to the ICU ($P = 0.004$) and require mechanical ventilation ($P = 0.002$). Adjustment for age, BMI, TBSA greater than or equal to or less than 20 per cent, total Glasgow coma score and admission HF showed that patients with 4-h delayed SD had an eight-fold increase in mortality (OR 8.27, 95 per cent c.i. 1.16 to 58.95; $P = 0.034$; [Table 2](#)). Deaths among patients with this phenotype also occurred at a faster rate (HR, 5.14, 95 per cent c.i. 1.07 to 24.82; $P = 0.041$; [Table 2](#); [Fig. 2b](#)). Transitions of patients between phenotypes from one time point to the next were common, occurring in 36 to 40 per cent of patients ([Table 3](#)).

Discussion

This study has characterized early fibrinolytic phenotypes in patients with burn injury using viscoelastic monitoring. Patients with thermal injury displayed three fibrinolytic phenotypes. At admission, 60.0 per cent of patients presented with PHYS, while 30.4 per cent were SD and 9.4 per cent displayed the HF phenotype. Using newly defined cut-offs for fibrinolytic phenotypes, Stettler and co-workers found that 71.0 per cent of severely injured patients exhibited a physiological phenotype, while 19.8 per cent were hypofibrinolytic and 9.2 per cent were hyperfibrinolytic early after trauma²⁷. At these cut-off levels, the distribution of phenotypes following trauma was comparable to those observed in the present study of patients with thermal injury.

The HF phenotype at admission was associated with increased 30-day mortality, consistent with previous reports for non-burn trauma^{2,3,27–37}. In the present study, patients with the admission HF phenotype also tended to die earlier, consistent with findings in other trauma populations^{30,31,36}.

Admission SD was not associated with increased mortality in the present study, as seen in some reports for non-burn trauma^{4,28,29,36,38}, although not in others^{2,3,27,33,34}. Persistent SD following trauma (e.g., SD at admission and at 7 days) has been shown to be a more reliable indicator of mortality than admission SD alone^{36,38,39}. Leeper and colleagues found that shutdown approximately doubled between the first and third hour following trauma in paediatric patients, and that hyperfibrinolysis decreased by nearly half³³. An increase in SD and a decrease in HF over the first few hours after burn injuries was also observed in the present study. It has been suggested that development of the SD phenotype may be associated with reperfusion during the resuscitation following trauma⁴⁰. As resuscitation takes place during the first hours after burn injury¹, this may have been a factor in the present study.

Although admission SD was not associated with increased mortality, delayed SD at 4 h and beyond was associated with increased mortality with about an eight-fold increase at 4 h after admission, independent of the admission HF phenotype ([Table 2](#)). Taken together, these data suggest that abnormal fibrinolysis during the early post-burn period is associated with increased mortality.

Table 1 Characteristics of the patients: admission fibrinolytic phenotypes

Variable	All	SD	PHYS	HF	P
Number of patients	115	35 (30.4)	69 (60.0)	11 (9.6)	—
Male	79 (68.7)	23 (65.7)	47 (68.1)	9 (81.2)	0.596
Age (years)*	40 (28–57)	38 (34–59)	40 (25–52)	57 (33–68)	0.164
Race/ethnicity					0.541
Caucasian	41 (35.7)	14 (40.0)	26 (37.7)	1 (9.1)	
African American	45 (39.1)	12 (34.3)	27 (39.1)	6 (54.5)	
Hispanic	9 (7.8)	3 (8.6)	5 (7.3)	1 (9.1)	
Other	20 (17.4)	6 (17.1)	11 (15.9)	3 (27.3)	
BMI*	26.7 (23.7–30.5)	27.4 (24.3–31.0)	26.5 (23.4–29.4)	24.8 (23.2–27.0)	0.225
Transport method					0.504
Helicopter	45 (39.1)	16 (45.7)	24 (34.8)	5 (45.5)	
Ambulance	70 (60.9)	19 (54.3)	45 (65.2)	6 (54.5)	
Time from injury to first blood draw (min)*	106 (78–170)	103 (91–190)	97 (71–154)	95 (60–175)	0.090
Percentage of TBSA burned*	13.0 (6.0–30.0)	18.0 (7.0–46.5)	12.0 (5.0–21.0) [†]	55.0 (8.0–93.0) [‡]	0.015
TBSA ≤20%	73 (63.5)	18 (51.4)	50 (72.5)	5 (45.5)	0.047
TBSA >20%	42 (36.5)	17 (48.6)	19 (27.5)	6 (54.5)	
Inhalation injury (n = 113)	28 (24.8)	12 (35.3)	12 (17.4)	4 (40.0)	0.071
Baux score at ED*	60.0 (39.5–82.0)	67.0 (48.5–86) [‡]	54.0 (37.0–73.0) [†]	79.6 (56.5–139.0) [‡]	0.015
GCS at ED score*	15 (13–15)	15 (9–15)	15 (15–15) [†]	12 (3–15) [‡]	0.023
ICU Admission	72 (62.6)	28 (80.0)	40 (58.0)	4 (36.4)	0.015
ICU stay (survivors, n = 55) (days)*	7 (2–17)	11 (3–22)	6 (1–14)	5	0.344
Mechanical ventilation	46 (40.0)	21 (60.0)	20 (29.0)	5 (45.5)	0.009
Ventilator duration (survivors, n = 26) (days)*	6 (2–14)	3 (1–11)	10 (5–17)	3	0.123
Duration of hospital stay (n = 94), days*	11 (6–20)	13 (8–25)	10 (3–19)	11 (8–16)	0.200
Total fluids at 24 h (ml)*	6838 (3435–11597)	9134 (3207–12687)	6220 (3310–11209)	5310 (3750–37310)	0.850
Mortality	21 (18.3)	8 (22.9)	7 (10.1)	6 (54.6)	0.001
Time to death (h) [*]	41.1 (5.4–284.7)	31.4 (7.7–287.5)	282.2 (41.1–482.8)	5.6 (2.2–22.0)	0.133
Cause of death					0.156
Burn shock	8 (38.1)	2 (25.0)	2 (28.6)	4 (66.7)	
Organ failure	6 (28.6)	1 (12.5)	3 (42.9)	2 (33.3)	
Other (cardiac arrest; brain death; sepsis)	7 (33.3)	5 (62.5)	2 (28.6)	0 (0.0)	
LY30 (%)*	1.5 (0.3–3.5)	0.0 (0.0–0.2) [‡]	2.2 (1.4–3.5) [†]	10.6 (9.4–14.4) [§]	<0.001
ACT*	121 (105–136)	113 (105–128)	121 (105–128)	125 (121–144)	0.131
Angle*	73.8 (69.4–77.2)	72.8 (64.4–77.7)	74.4 (71.6–76.9)	64.7 (54.8–76.8)	0.088
MA*	61.8 (56.0–65.0)	60.4 (54.5–64.0) [‡]	62.5 (59.3–66.3) [†]	54.2 (44.0–62.2) [‡]	0.009
PT at admission (n = 87) (sec)*	13.3 (12.9–14.1)	13.2 (12.9–13.9)	13.4 (13.0–14.2)	13.3 (12.6–42.5)	0.606
INR at admission (n = 87)*	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.1 (1.0–1.1)	1.0 (1.0–1.2)	0.121
INR >1.2	4 (4.6)	0 (0.0)	3 (5.4)	1 (16.7)	0.210
Platelet count (× 10³/ul)*	259 (210–299.5)	244.5 (200–292.5)	256.5 (210–300)	282 (255–340)	0.387

Values in parentheses are percentages unless otherwise stated; *values are median (i.q.r.). SD, fibrinolytic shutdown; PHYS, physiologic; HF, hyperfibrinolytic; ED, emergency department; TBSA, total body surface area; GCS, total Glasgow coma scale; ICU, intensive care unit; LY30, Clot lysis at 30 min after maximum clot strength; ACT, activated clotting time; MA, maximum amplitude; PT, prothrombin time; INR, international normalized ratio. P values were calculated with χ^2 or Fisher's exact test or Kruskal–Wallis test. For pairwise comparison, †, ‡, § differ using Mann–Whitney U test with a Bonferroni correction (adjusted P = 0.0167).

Considering the effects of admission HF, the finding that delayed HF was not associated with mortality was unexpected, but raises the possibility that, if early HF could be prevented, reversed or delayed, outcomes may be improved. Of the 10 patients who developed HF after admission, only one died. It is possible that delayed HF may occur by different mechanisms from admission HF. Contributing factors may include the initial injury or early resuscitation, but not sepsis which would be expected to occur later. It is also possible that the difference may lie in the patient's innate ability to buffer the fibrinolytic response. Some patients have a greater innate resistance to tissue plasminogen activator³⁴. This may provide some protection against HF during the early post-burn period, but may also be a factor in development of delayed SD. This requires further study to understand the mechanisms involved.

Patients that exhibited either the HF or SD phenotypes at admission had larger burn TBSA. Previous studies have documented a greater degree of fibrinolytic activation associated with increasing burn size^{3,8,11}. Abnormal phenotypes have not consistently been associated with higher injury severity in adult non-burn trauma, with various reports of either no difference or increased injury severity associated with SD or HF^{2,3,29,36,38}, although in children, Leeper and colleagues observed that the Injury Severity Score (ISS) was higher in patients with fibrinolytic shutdown⁴. Differences between blunt and penetrating trauma have also been observed, with hypofibrinolysis associated more with blunt trauma^{3,4}. Experimental studies have demonstrated that extensive tissue injury is associated with suppression of fibrinolysis, while shock is associated with hyperfibrinolysis^{41–43}. Burn trauma may be unique in that there appears to be a strong relationship between extent of injury and frequency of abnormal

Table 2 Likelihood of 30-day mortality and time to death for fibrinolytic phenotype at admission

Variable	Odds ratio	P	Hazard ratio	P
Sex, female versus male	0.64 (0.21–1.89)	0.415	0.72 (0.26–1.96)	0.516
Ethnicity				
African American versus European American	1.46 (0.47–4.53)	0.514	1.61 (0.57–4.55)	0.369
Hispanic versus European American	—	—	—	—
Other versus European American	2.50 (0.67–9.08)	0.164	2.18 (0.70–6.76)	0.178
Age at injury, each increase of 1 year	1.06 (1.03–1.10)	<0.001	1.05 (1.02–1.08)	<0.001
BMI, ≥ 30 versus <30 kg/m²	0.24 (0.05–1.08)	0.063	0.95 (0.90–1.02)	0.138
Total percentage TBSA burn, >20 versus $\leq 20\%$	29.33 (6.34–135.57)	<0.001	12.14 (2.78–52.93)	<0.001
Inhalation injury, yes versus no	8.36 (2.85–24.51)	<0.001	4.50 (1.75–11.53)	0.002
GCS, each increase of 1	0.80 (0.72–0.88)	<0.001	0.85 (0.79–0.92)	<0.001
Transport, helicopter versus ambulance	0.52 (0.20–1.34)	0.173	1.45 (0.61–3.43)	0.400
Admission fibrinolytic phenotypes				
SD versus PHYS	2.62 (0.86–7.97)	0.089	1.94 (0.70–5.37)	0.203
HF versus PHYS	10.63 (2.57–44.00)	0.001	8.10 (2.63–24.96)	<0.001
HF versus SD	4.05 (0.97–16.84)	0.054	4.18 (1.36–12.80)	0.012
Delayed fibrinolytic phenotype at 4 h				
SD versus PHYS	9.84 (2.03–47.65)	0.005	5.60 (1.25–25.13)	0.024
Adjusted model:				
Admission fibrinolytic phenotype*				
SD versus PHYS	2.13 (0.46–9.83)	0.323	1.89 (0.63–5.67)	0.256
HF versus PHYS	12.61 (1.12–142.57)	0.041	4.95 (1.17–20.95)	0.030
HF versus SD	5.92 (0.50–70.03)	0.158	2.62 (0.60–11.51)	0.202
Delayed fibrinolytic phenotype†				
SD versus PHYS	8.27 (1.16–58.95)	0.034	5.14 (1.07–24.82)	0.041

Values in parentheses are 95% confidence intervals. SD, fibrinolytic shutdown; PHYS, physiologic; HF, hyperfibrinolytic. * Adjusted for age, BMI, total body surface area (TBSA) \leq / $>$ 20 per cent, total Glasgow coma scale (GCS) and inhalation injury; † adjusted for age, BMI, TBSA \leq / $>$ 20 per cent, total GCS and hyperfibrinolysis at admission (H0). ED, emergency department.

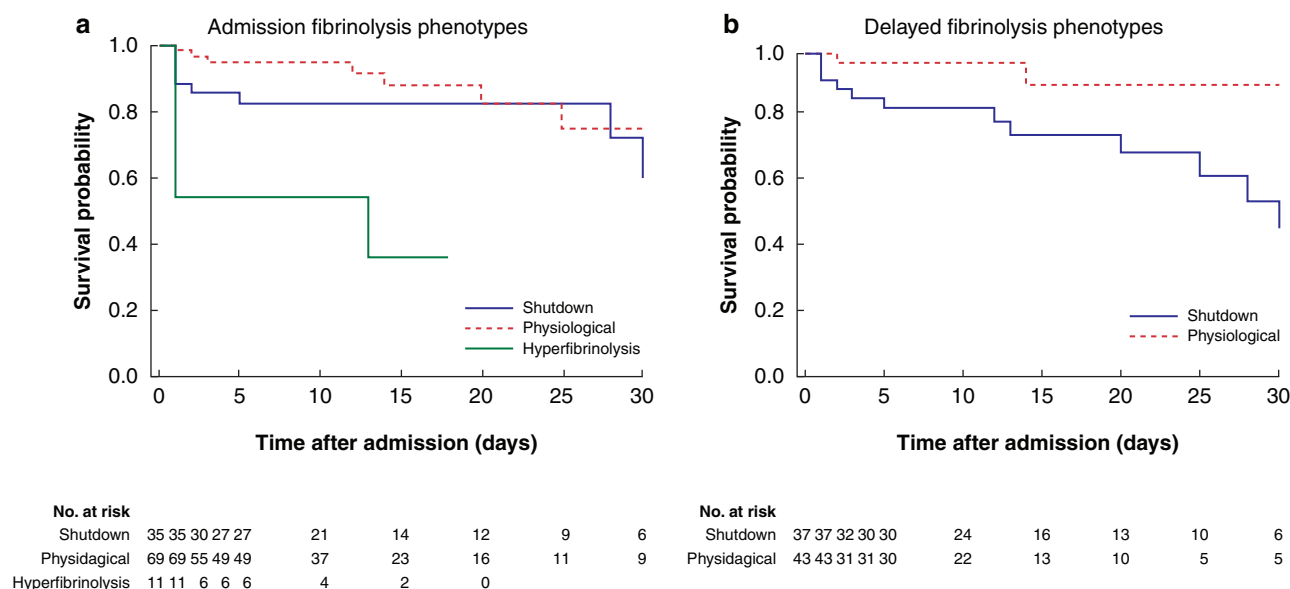


Fig. 2 Influence of admission fibrinolytic phenotypes and delayed fibrinolytic phenotypes on 30-day mortality

Kaplan-Meier plots. **a** Estimated 30-day survival rate by fibrinolytic phenotypes for patients that displayed hypofibrinolysis (shutdown), physiological fibrinolysis, or hyperfibrinolysis at admission (admission fibrinolytic phenotypes). Log-rank $P < 0.001$. Hazard ratios (95 per cent c.i.): shutdown versus physiological, 1.89 (0.63–5.67); hyperfibrinolysis versus physiological, 4.95 (1.17–20.95); hyperfibrinolysis versus shutdown 2.62 (0.60–11.51). **b** Estimated 30-day survival rate in patients who displayed the shutdown or physiological fibrinolytic phenotypes 4 h after admission (delayed fibrinolytic phenotype). Log-rank $P = 0.010$. Hazard ratio (95% c.i.) 5.15 (1.07–24.82).

fibrinolysis. It is possible that this relationship exists because TBSA is a more direct measure of extent of injury than ISS.

INR did not differ among fibrinolytic phenotypes in the present study. Principal component analyses of both viscoelastic assays and coagulation factors have demonstrated that the two

systems can behave differently, are measured differently and represent independent but integrated systems contributing to overall haemostatic balance^{44,45}. Some studies in burn patients have reported prolonged PT/INR^{8,11,15} in the presence of fibrinolytic activation, while others have not^{6,10}. Some have reported

Table 3 Hyperfibrinolytic and shutdown phenotypes between 0 and 12 hours after admission: incidence and mortality

	Hour 0 (n = 115)	Hour 2 (n = 97)	Hour 4 (n = 85)	Hour 8 (n = 74)	Hour 12 (n = 70)
Hyperfibrinolytic phenotype					
Patients with HF	11 (9.6)	5 (5.2)	5 (5.9)	4 (5.4)	1 (1.4)
Mortality in HF patients	6 (55.5)	2 (40)	0 (0)	0 (0)	0 (0)
P for comparison with no HF	0.005	0.231	0.585	0.999	0.999
Shutdown phenotype					
Patients with SD	35 (30.4)	43 (44.3)	37 (43.5)	27 (36.5)	31 (44.3)
Mortality in patients with SD	8 (22.9)	10 (23.3)	12 (32.4)	9 (33.3)	10 (32.3)
P for comparison with no SD	0.399	0.288	<0.001	0.006	0.002
TBSA burn					
≤20%	73 (63.5)	62 (63.9)	55 (64.7)	52 (70.3)	46 (65.7)
>20%	42 (36.5)	35 (36.1)	30 (35.3)	22 (29.7)	24 (34.3)
P compared with Hour 0	—	0.947	0.858	0.336	0.758
Patient transitions among phenotypes	—	35 (36.1)	31 (39.2)	27 (40.3)	23 (38.3)
Total with abnormal phenotype (HF or SD)	46 (40.0)	49 (50.0)	43 (50.0)	31 (41.3)	33 (46.5)

Values in parentheses are percentages. HF, hyperfibrinolytic; SD, shutdown; TBSA, total body surface area. P values were calculated with χ^2 or Fisher's exact test.

elevated INR in both hypo- and hyperfibrinolytic phenotypes^{3,4}, while others have not². ACT did not differ among phenotypes (Tables 1 and 3), although MA was reduced in HF, similar to the finding in a large cohort of patients with non-burn trauma³⁶.

Fibrinolytic activation after burn injury has been well documented⁵. Higher levels of fibrinolytic activation are associated with larger burn size, organ failure and mortality. Those with overt disseminated intravascular coagulation, as diagnosed using measures of both coagulation and fibrinolysis, have greater risk of organ failure and mortality^{6,10}. While coagulation and fibrinolytic activation were observed in these studies, it was noted that there was a relatively greater increase in fibrinolytic inhibitors than fibrinolytic activators. It was hypothesized that over-activation of coagulation combined with relatively inhibited fibrinolysis, resulted in diffuse fibrin deposition, leading to organ failure^{6,10}. The results of the current study are consistent with these findings and suggest that burn injury induces early fibrinolytic activation, related to the degree of injury, followed by development of fibrinolytic inhibition in a subset of patients.

As admission HF can be recognized within 1–2 h of injury and delayed SD recognized within 4 h of burn injury using TEG, a window of opportunity for treatment may exist as noted in other populations³³. It may be possible to titrate antifibrinolytic or pro-fibrinolytic drugs to alter the development or time course of abnormal phenotypes. Alternatively, early plasma transfusion may be an option, considering its potential capacity to 'buffer' the fibrinolytic system both *in vitro* and *in vivo*^{43,46}. Haemostatic resuscitation, including plasma, has been shown to reverse HF in paediatric trauma patients³⁹.

This study has limitations. Phenotypes were based solely on TEG results, without biochemical confirmation of

fibrinolytic status. Potential mechanisms that led to the TEG phenotypes could not be assessed. Future research, matching biomarkers with viscoelastic analyses in burn patients are needed. There were some missing data points in the TEG data. It is possible that the true starts of delayed phenotypes were missed, as the first available time points were assigned. Across sampling times, TBSA was similar (Table 3) so it seems unlikely that the missing samples systematically impacted results for any one patient group or phenotype preferentially.

Three fibrinolytic phenotypes that are independently related to mortality evolve over time in patients with burn injury. Identification and possible modification of these phenotypes based on early viscoelastic monitoring may be valuable in the management of patients with thermal injury.

Collaborators

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Supplementary material

Supplementary material is available at BJS Open online.

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